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# Nuclear data relevant to the production and application of diagnostic radionuclides

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**Summary.** The types of nuclear data and their quality required in the production and application of diagnostic radionuclides are outlined. The radioactive decay data determine the suitability of a radioisotope for *in vivo* tracer studies, both from the imaging and internal radiation dose considerations. The nuclear reaction cross section data allow optimisation of production routes. Both reactors and cyclotrons are used for production purposes. The nuclear data needed in the two cases and their present status are discussed. Special attention is paid to radionuclides suitable for emission tomography (PET and SPECT). The controversy about *reactor* vs *cyclotron* production of the widely used $^{99}Mo/^{99m}Tc$ generator system is discussed. Some special considerations in cyclotron production of radionuclides are outlined. The need of accurate data near reaction thresholds, the constraint of available particles and their energies at a small cyclotron, the influence of increasing incident particle energy, and the formation of isomeric impurities are discussed in detail. The role of nuclear model calculations in predicting unknown data is considered.

## 1. Introduction

A medically related radioisotope is classified as a *diagnostic* or a *therapeutic* radionuclide, depending on its decay properties. In this article the diagnostic radioisotopes in general, and their production data in particular, are treated. The major criteria for diagnostic use are:

– suitable physical properties, i.e. a high detection efficiency for the radionuclide, compatible with the lowest possible radiation dose to the patient
– suitable biochemical properties, especially organ selectivity and comptability with the bio-kinetics.

As far as physical properties are concerned, the half-life should be short (between a few minutes and a few hours) and the decay should occur preferably via IT, EC or $\beta^+$ emission. Furthermore, the specific radioactivity of the final product should be rather high. In general, the diagnostic radioisotopes are classified into two groups, namely $\gamma$-emitters (e.g. $^{67}Ga$, $^{111}In$, $^{201}Tl$, etc.) and $\beta^+$ emitters (e.g. $^{15}O$, $^{18}F$, etc.). If the radioisotope emits a single $\gamma$-ray, the detection technique called Single Photon Emission Computed Tomography (SPECT) can be used; in the case of $\beta^+$ emitters, the use of Positron Emission Tomography (PET) is very advantageous. The two techniques (SPECT and PET) are often collectively termed as *emission tomography*. By virtue of its quantitative nature, rapidity and higher resolution, PET is superior to SPECT. However, the latter finds much wider use due to considerably lower costs of radionuclides, instrumentation and operation. A detailed description of the two diagnostic techniques is given elsewhere in this issue (cf. contribution by Herzog).

The biochemical properties have little relevance to nuclear data. They depend upon the functional group of the molecule to which the radioisotope has been attached. Evidently, for fast biochemical phenomena, like glucose or oxygen uptake, short-lived radioisotopes are suitable, whereas for slower processes, like protein synthesis, somewhat longer-lived radioisotopes are needed.

## 2. Radioactive decay data: internal radiation dose calculation

As mentioned above, the physical properties determine the choice of a radioisotope for medical application. In internal radiation dose calculation, i.e. calculation of the dose to an organ delivered by the administered radionuclide, however, both decay data and biological behaviour of the compound labelled with the radioisotope need to be considered. The effective half-life of the radiopharmaceutical in the organ is thus a combination of the physical half-life and the biological half-life.

The available information on decay data is extensive, at least for the most commonly used PET and SPECT radioisotopes. The types of data needed in internal radiation dose calculations have been outlined (cf. Introductory chapter by Qaim). The methods of internal dose calculation have received extensive attention and well-known computer codes, known as MIRD codes, are now available. A discussion of the dose calculation in diagnostic studies using PET and SPECT is given elsewhere is this issue (cf. contribution by

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Herzog on this topic). Here it needs to be pointed out that the criterion of minimum dose in diagnostic studies puts a heavy demand on the radionuclidic purity of the radiopharmaceutical. If some impurity is present, especially having a long half-life and emitting corpuscular radiation, it will lead to additional radiation dose. Thus the production method should be chosen such that the product radionuclide contains the lowest possible impurity. In general, the isotopic impurities are controlled by a selection of the relevant production data, and the non-isotopic impurities by a clean chemical separation. The MIRD calculations are generally based on the assumption that the radionuclide under consideration is of the highest possible purity.

In recent years, accurate dosimetric considerations have demanded a more detailed information on the low energy but high intensity corpuscular radiation (such as conversion and Auger electrons) associated with some diagnostic radionuclides (e.g. those decaying by EC or IT). This low energy radiation is not detectable with the instrumentation used in nuclear medicine but causes additional dose. Some new efforts are therefore under way to examine conversion coefficients of nuclear transitions related to SPECT radioisotopes.

## 3. Nuclear reaction cross sections and production yields

The nuclear reaction cross sections are of considerable importance in optimising the production process of a radioisotope (cf. Introductory chapter by Qaim). In principle, the well-known activation equation is applicable to all activation processes, whether induced by neutrons or charged particles. In practice, however, there are distinct differences since the neutrons generally show a spectral distribution whereas the charged particles rapidly lose energy while traversing a medium. In the following, the nuclear data relevant to the production of radioisotopes in a reactor and at a cyclotron are discussed separately.

### 3.1 Production of radioisotopes in a nuclear reactor

#### 3.1.1 Nuclear reactions

The production of radionuclides in a nuclear reactor has been under constant review for the last four decades [cf. 1]. In this article mainly the nuclear data aspects are considered. The relevant nuclear processes are described below.

*$(n, \gamma)$ reaction*

This is the most commonly occurring reaction in a nuclear reactor. Since no reaction threshold is involved, this process can be induced by thermal, epithermal as well as fast neutrons, although in general the cross section is most relevant for thermal neutrons. A few examples of radioisotopes produced via this method are given in Table 1. Among them are $^{99}$Mo, $^{125}$Xe and $^{131m,g}$Te, the parents of the commonly used radionuclides $^{99m}$Tc, $^{125}$I and $^{131}$I, respectively. The major advantage of the procedure lies in the simple methodology, and the main disadvantage in the low specific radioactivity. The latter is improved to some extent via Szilard-Chalmer´s process or via generator preparation, i.e. by using the decay product of an $(n, \gamma)$ reaction product.

*Inelastic scattering*

In recent years a few isomeric states have been activated via the $(n, n'\gamma)$ process, especially those having high nuclear spins. Some of those radionuclides, for example $^{117m}$In, $^{119m}$Sn and $^{195m}$Pt are produced in higher specific radioactivity via the $(n, n'\gamma)$ process than via the $(n, \gamma)$ reaction [cf. 2].

*Sequential neutron capture*

Occasionally a radioisotope may be produced via a sequential capture of two neutrons (cf. Table 1). The process is, however, of limited use since it occurs only in a high flux reactor. It appears to be of special advantage in the region of rare earths where the neutron capture cross sections are very high.

*(n, fission) process*

Like the $(n, \gamma)$ reaction, it is also a commonly used process. In general, products lying on one of the two mass-yield peaks of the fission process can be advantageously produced. Two very important medical radionuclides, namely $^{99}$Mo and $^{131}$I, are produced via the fission of $^{235}$U (cf. Table 1). The method is of great advantage and leads to no-carrier-added products, i.e. products of very high specific radioactivity. The main disadvantage, however, is the extensive chemical processing involved.

*(n, z) process*

The emission of charged particles in neutron induced reactions is also utilized to produce some special radioisotopes. In general, these reactions occur only in the light mass region where the reaction thresholds are low and the competition between charged particle and neutron emission is in favour of the former. Some examples are given in Table 1. The method is of considerable advantage since the products are of high specific radioactivity. The cross sections are, however, generally low, except for the formation of tritium and $^{14}$C. The latter two radionuclides are almost exclusively produced via the $(n, z)$ process.

*Secondary reactions*

In certain cases the charged particle emitted in a nuclear reaction may induce a secondary reaction on a neighbouring nucleus. Two such cases are mentioned in Table 1. The production of $^{18}$F via the reaction sequence $^{6}\mathrm{Li}(n, \alpha)^{3}\mathrm{H} \rightarrow {}^{16}\mathrm{O}(t, p)^{18}\mathrm{F}$ had been in use for quite some time. The major problems were the relatively low yields of $^{18}$F and presence of tritium impurity. In recent years the cyclotron production of $^{18}$F has completely superseded its production in a reactor. Similarly, $^{28}$Mg production is now also done more commonly at a medium-energy cyclotron.

It is understood that the use of a secondary reaction in medical radionuclide production demands a careful consideration of the cross section of the primary reaction, the energy spectrum of the emitted charged particle, as well as the

**Table 1.** Commonly used nuclear reactions for the production of some radioisotopes in a nuclear reactor.

| Radio-nuclide | $T_{1/2}$ | Mode of decay (%) | Main $\gamma$-ray energy in keV (%) | Production reaction | Cross section in barn* |
|---|---|---|---|---|---|
| | | | **$(n, \gamma)$ reaction** | | |
| $^{24}$Na | 15.0 h | $\beta^-$ (100) | 1369 (100)<br>2754 (99.9) | $^{23}$Na$(n, \gamma)$ | 0.53 |
| $^{32}$P | 14.3 d | $\beta^-$ (100) | | $^{31}$P$(n, \gamma)$ | 0.18 |
| $^{35}$S | 87.5 d | $\beta^-$ (100) | | $^{34}$S$(n, \gamma)$ | 0.29 |
| $^{42}$K | 12.4 h | $\beta^-$ (100) | 1525 (18.8) | $^{41}$K$(n, \gamma)$ | 1.46 |
| $^{51}$Cr | 27.7 d | EC (100) | 320 (9.8) | $^{50}$Cr$(n, \gamma)$ | 15.90 |
| $^{64}$Cu | 12.7 h | $\beta^+$ (18); EC (45);<br>$\beta^-$ (37) | | $^{63}$Cu$(n, \gamma)$ | 4.50 |
| $^{75}$Se | 119.8 d | EC (100) | 136 (59.0)<br>265 (59.2)<br>401 (11.6) | $^{74}$Se$(n, \gamma)$ | 46.00 |
| $^{99}$Mo | 66.0 h | $\beta^-$ (100) | 140 (90.7)<br>740 (12.1) | $^{98}$Mo$(n, \gamma)$ | 0.13 |
| $^{125}$Xe | 16.9 h | $\beta^+$(0.7); EC (99.3) | 188 (54.9)<br>243 (28.8) | $^{124}$Xe$(n, \gamma)$ | 165.00 |
| $^{131m,g}$Te† | 30.0 h<br>25.0 min | IT (22); $\beta^+$ (78)<br>$\beta^-$ (100) | 774 (38.1)<br>150 (68.9) | $^{130}$Te$(n, \gamma)$ | 0.23 |
| $^{153}$Sm | 46.3 h | $\beta^-$ (100) | 103 (28.3) | $^{152}$Sm$(n, \gamma)$ | 206.00 |
| $^{186}$Re | 89.2 h | $\beta^-$ (92.2); EC (7.8) | 137 (8.5) | $^{185}$Re$(n, \gamma)$ | 114.00 |
| | | | **Sequential neutron capture** | | |
| $^{32}$Si | 172.0 a | $\beta^-$ (100) | | $^{30}$Si$(n, \gamma)$ $^{31}$Si$(n, \gamma)$ (2.6 h) | 0.11; 0.3 |
| $^{166}$Dy† | 81.5 h | $\beta^-$ (100) | 82 (13.0) | $^{164}$Dy$(n, \gamma)^{165}$Dy$(n, \gamma)$ (2.4 h) | 2700; 3500 |
| $^{188}$W† | 69.0 d | $\beta^-$ (100) | 291 (0.4) | $^{186}$W$(n, \gamma)^{187}$W$(n, \gamma)$ (23.7 h) | 36; 70 |
| | | | **$(n,$ fission$)$ process** | | |
| $^{90}$Sr† | 28.6 a | $\beta^-$ (100) | | $^{235}$U$(n, f)$ | $Y_{cum}$: 5.89% |
| $^{99}$Mo† | ——— see above ——— | | | $^{235}$U$(n, f)$ | $Y_{cum}$: 6.14% |
| $^{131}$I | 8.0 d | $\beta^-$ (100) | 364 (81.2)<br>637 (7.3) | $^{235}$U$(n, f)$ | $Y_{cum}$: 2.84% |
| | | | **$(n,z)$ reaction** | | |
| $^{3}$H | 12.3 a | $\beta^-$ (100) | | $^{6}$Li$(n, \alpha)$ | 940 |
| $^{14}$C | 5730 a | $\beta^-$ (100) | | $^{14}$N$(n, p)$ | 1.8 |
| $^{32}$P | ——— see above ——— | | | $^{32}$S$(n, p)$ | 0.07 |
| $^{35}$S | ——— see above ——— | | | $^{35}$Cl$(n, p)$ | 0.08 |
| $^{37}$Ar | 35.0 d | EC (100) | | $^{40}$Ca$(n, \alpha)$ | 0.03 |
| | | | **Secondary reactions** | | |
| $^{18}$F | 109.6 min | $\beta^+$ (97); EC (3) | | $^{6}$Li$(n, \alpha)^{3}$H $\rightarrow$ $^{16}$O$(t, p)^{18}$F | |
| $^{28}$Mg | 20.9 h | $\beta^-$ (100) | 401 (36)<br>1342 (54) | $^{6}$Li$(n, \alpha)^{3}$H $\rightarrow$ $^{26}$Mg$(t, p)^{28}$Mg | |

* Capture cross sections as well as the $^{6}$Li$(n, \alpha)$ and $^{14}$N$(n, p)$ cross sections are for thermal neutrons. Other $(n, z)$ cross sections are fission neutron spectrum averaged values. The fission yields are cumulative yields ($Y_{cum}$). For the secondary reactions only production yields have been reported in the literature.

† Decay products are of interest: $^{90}$Sr $\rightarrow$ $^{90}$Y; $^{99}$Mo $\rightarrow$ $^{99m}$Tc; $^{131m,g}$Te $\rightarrow$ $^{131}$I; $^{166}$Dy $\rightarrow$ $^{166}$Ho; $^{188}$W $\rightarrow$ $^{188}$Re.

absorption profile of the particle in the surrounding medium. A chemical compound or an alloy form is very suitable for production purposes, for example, $Li_2CO_3$ to produce $^{18}$F and Li/Mg alloy to produce $^{28}$Mg.

### 3.1.2 Chemical processing and applications

Though only indirectly related to the problem of nuclear data, a brief mention should be made of the techniques and methods used to obtain the desired radionuclide in a suitable form after activation in a nuclear reactor. In general, after the irradiation, an extensive chemical processing is mandatory, especially if the fission process is utilized for production purposes. The demands on the purity are very stringent, particulary with regard to the content of $\alpha$-emitting impurities. An example is the separation of $^{99}$Mo from $^{235}UAl_3$-alloy. The chemically separated $^{99}$Mo is used to prepare a *generator* system. This consists of loading the $^{99}$Mo activity on an $Al_2O_3$ column and milking off the decay product $^{99m}$Tc periodically by elution with saline.

It is worth mentioning that the $^{99}$Mo/$^{99m}$Tc generator is the most commonly used system in diagnostic

nuclear medicine. Due to the ideal imaging properties of $^{99m}$Tc with SPECT, about 80% of all nuclear medical procedures are performed worldwide with it. The generator form makes the availability of $^{99m}$Tc easy; its specific radioactivity is very high. The product is used directly for labelling biomolecules. In fact several kits have been developed which require a simple addition of the eluted saline containing $^{99m}$Tc to obtain a particular radiopharmaceutical.

As far as nuclear data are concerned, constructing a generator system demands a good knowledge of the decay properties of the two radioisotopes concerned. In particular, the half-lives are important, but the shielding requirements also demand a knowledge of the corpuscular and electromagnetic radiation emitted in the decay of the two genetically related radioisotopes as well as the impurities, if any.

Many of the reactor-produced corpuscular radiation emitting radionuclides are used in therapy (cf. contribution by Qaim on this topic, this issue). Some radioisotopes find application in tracer studies related to industrial processes, radioagronomy and enviromental phenomena. The soft radiation emitting radionuclides $^{3}$H, $^{14}$C and $^{125}$I are extensively used in investigations involving *in vitro* methods.

### 3.1.3 Status of production cross sections

The status of neutron induced reaction cross sections is generally good, mainly due to the energy-related programmes. Data on the three types of processes commonly used in medical radioisotope production, viz. $(n, \gamma)$, $(n$,fission) and $(n, z)$, are well compiled [cf. 3–6], well evaluated using nuclear model calculations [cf. 7–9], and well documented (see e.g. contribution by Schwerer and Oblozinsky, this issue). For many reactions, data validation has also been performed by comparing integral yield measurements in a fission spectrum with those integrated from the measured $(n, x)$-excitation functions (for a fission spectrum distribution).

For the less commonly used $(n, n'\gamma)$ and double neutron capture processes, it is occasionally necessary to perform new measurements or to evaluate the existing data, especially if they show large discrepancies.

## 3.2 Production of radioisotopes at a cyclotron

The production of radioisotopes at cyclotrons has been extensively discussed in many review articles, monographs and books. A critical analysis of the nuclear data problems was first done at Jülich [10]. The emphasis in this section of the present article is on new aspects of nuclear data research relevant to cyclotron production of radionuclides.

### 3.2.1 Cyclotrons for applications

Over the last two decades, several types of cyclotrons and accelerators have been developed to meet the specific demands of radionuclide production; a summary is given in Table 2. The presentation is an updated form of an earlier classification [11]. The smallest accelerator is a single particle machine with $E_{\mathrm{d}} \leq 4$ MeV, i.e. below the breakup threshold of the deuteron (to avoid neutron background). It is used exclusively in a hospital environment to produce $^{15}$O. The next stage accelerator is also a single particle negative ion machine with $E_{\mathrm{p}} \leq 11$ MeV or 12 MeV and can be used to produce the four major $\beta^+$ emitters, viz. $^{11}$C, $^{13}$N, $^{15}$O and $^{18}$F, although the absence of the deuteron beam is somewhat disadvantageous regarding the production of $^{15}$O, and the rather low proton energy gives low yield of $^{13}$N. The next higher group of machines is generally a two particle machine with $E_{\mathrm{p}} \leq 20$ MeV and $E_{\mathrm{d}} \leq 10$ MeV. It is ideally suited for the production of commonly used PET radioisotopes. The higher energy machines have capabilities of producing many more radioisotopes, in particular when besides $p$ and $d$, also $^{3}$He and $\alpha$-particle beams are available. On the other hand, when energies above 100 MeV are under consideration, only the proton beam is of interest.

### 3.2.2 Cyclotron products and data needs

In diagnostic studies, the cyclotron products exhibit considerable advantages over the reactor products. The specific radioactivity is high and the radiation dose is low. Furthermore, they are often more suitable for emission tomography. Since in many cases they may be easily attached to a biomolecule, they are very useful for investigating regional physiological functions.

**Table 2.** Types of accelerators routinely used for radioisotope production.

| Classification | Characteristics | Energy [MeV] | Major radionuclides produced |
|---|---|---|---|
| Level I | single particle* $(d)$ | $< 4$ | $^{15}$O |
| Level II | single particle $(p)$ | $\leq 11$ | $^{11}$C, $^{13}$N, $^{15}$O, $^{18}$F |
| Level III | single or two particle $(p, d)$ | $\leq 20$ | $^{11}$C, $^{13}$N, $^{15}$O, $^{18}$F ($^{123}$I, $^{67}$Ga, $^{111}$In) |
| Level IV | single or multiple particle $(p, d, ^{3}\mathrm{He}, ^{4}\mathrm{He})$ | $\leq 40$ | $^{38}$K, $^{73}$Se, $^{75-77}$Br, $^{123}$I, $^{81}$Rb ($^{81}$Kr), $^{67}$Ga, $^{111}$In, $^{201}$Tl, $^{22}$Na, $^{57}$Co |
| Level V | single or multiple particle $(p, d, ^{3}\mathrm{He}, ^{4}\mathrm{He})$ | $\leq 100$ | $^{28}$Mg, $^{72}$Se ($^{72}$As), $^{82}$Sr ($^{82}$Rb), $^{117m}$Sn, $^{123}$I |
| Level VI | single particle $(p)$ | $\geq 200$ | $^{26}$Al, $^{32}$Si, $^{44}$Ti, $^{67}$Cu, $^{68}$Ge ($^{68}$Ga), $^{82}$Sr ($^{82}$Rb), $^{109}$Cd, $^{95m}$Tc, etc. |

* A small linear two particle accelerator $(p, d)$ has also been suggested.

**Table 3.** Routine methods of production of some commonly used positron emitters [cf. 12, 13].

| Radionuclide | $T_{1/2}$ | Mode of decay (%) | Main $\gamma$-ray energy in keV (%) | Production data | | |
|---|---|---|---|---|---|---|
| | | | | Nuclear reaction* | Energy range (MeV) | Thick target yield MBq(mCi)/μA · h |
| $^{11}$C | 20.4 min | $\beta^+$ (99.8)<br>EC (0.2) | 511 (199.6) | $^{14}$N ($p$, $\alpha$) | 13 → 3 | 3820 (103) |
| $^{13}$N | 10.0 min | $\beta^+$ (100) | 511 (200) | $^{16}$O ($p$, $\alpha$) | 16 → 7 | 1665 (45) |
| $^{15}$O | 2.0 min | $\beta^+$ (99.9)<br>EC (0.1) | 511 (199.8) | $^{14}$N ($d$, $n$)<br>$^{15}$N ($p$, $n$) | 8 → 0<br>10 → 0 | 2368 (64)<br>2220 (60) |
| $^{18}$F | 109.6 min | $\beta^+$ (97)<br>EC (3) | 511 (194) | $^{18}$O ($p$, $n$)<br>$^{20}$Ne ($d$, $\alpha$) | 16 → 3<br>14 → 0 | 2960 (80)<br>1110 (30) |
| $^{68}$Ge<br>↓ (generator) | 271 d | EC (100) | | RbBr ($p$, spall)<br>$^{69}$Ga ($p$, $2n$) | 800, 500 | 0.15 (0.0004) |
| $^{68}$Ga | 68 min | $\beta^+$ (90)<br>EC (10) | 511 (180)<br>1077 (3) | | | |
| $^{82}$Sr<br>↓ (generator) | 25 d | EC (100) | | Mo ($p$, spall)<br>$^{85}$Rb ($p$, $4n$) | 800<br>60 → 40 | 3.7 (0.1)<br>14.8 (0.4) |
| $^{82}$Rb | 1.3 min | $\beta^+$ (96)<br>EC (4) | 511 (192)<br>776 (13.4) | | | |

* Evaluated excitation functions of all the reactions listed here (except the spallation process) are now available in [14]. The yields given here are generally in agreement with those reported in [14].

Due to a variety in the available charged particles and the broad spectrum of energies involved, the nuclear data needs in cyclotron production of radioisotopes are much more intense than those in reactor production. Some salient groups of radionuclides are treated in detail below.

*Positron emitters*

Most of the PET studies to date are carried out with the four short-lived organic positron emitters, viz. $^{11}$C($T_{1/2}$ = 20 min), $^{13}$N($T_{1/2}$ = 10 min), $^{15}$O($T_{1/2}$ = 2 min) and $^{18}$F($T_{1/2}$ = 110 min). The former three radionuclides are generally used on site of production. $^{18}$F, on the other hand, is suitable for transport to nearby PET centres without a cyclotron. There is also considerable interest in $^{68}$Ga($T_{1/2}$ = 68 min) and $^{82}$Rb($T_{1/2}$ = 1.3 min), which are obtained via longer-lived generator parents. The routine production methods of the commonly used $\beta^+$ emitters are summarized in Table 3 [cf. 12, 13].

The organic $\beta^+$ emitters are generally produced using low energy nuclear reactions like ($p$, $n$), ($p$, $\alpha$), ($d$, $n$), ($d$, $\alpha$), etc. and a small-sized cyclotron is adequate for production purposes. The excitation functions have been measured in several laboratories. The cross sections show strong fluctuations, probably due to the population of known discrete levels of the product nucleus. The nuclear model calculations cannot *a priori* describe such excitation functions. In a recent attempt to evaluate the existing data under the auspices of an IAEA-CRP [14], therefore, only statistical fitting procedures were employed. The recommended curve for the $^{16}$O($p$, $\alpha$)$^{13}$N reaction, taken from [14], is shown in Fig. 1 as an example. The integated yields of the products calculated from the excitation functions, however, show smooth curves, i.e. in the production process the nuclear structure effects are washed out [12].

Several $\beta^+$ emitting radiopharmaceuticals are now routinely used in diagnostic nuclear medicine [cf. 13]. Of major interest is the product 2-[$^{18}$F]fluoro-2-deoxy-D-glucose, commonly known as FDG. Its synthesis was developed at Jülich [15]. Curie amounts of this radiopharmaceutical are now available using automated synthesizers. The clinical applications of several PET tracers are discussed elsewhere in this issue (cf. contribution by Herzog on functional imaging).

The generator produced $\beta^+$ emitters find application mostly in PET studies at centres without a cyclotron. The parent isotopes of the two most commonly used systems (see Table 3), namely $^{68}$Ge and $^{82}$Sr, are rather difficult to produce. Although cross section data on the relevant ($p$, $xn$) reactions have been measured and also recently evaluated [14], due to targetry problems, in both cases the method of choice is the spallation process [cf. 16, 17]. The production yields are known.

The number of potentially interesting longer-lived research related $\beta^+$ emitters is relatively large, but their relative importance keeps on changing. The production of those radionuclides often demands larger cyclotrons. In many

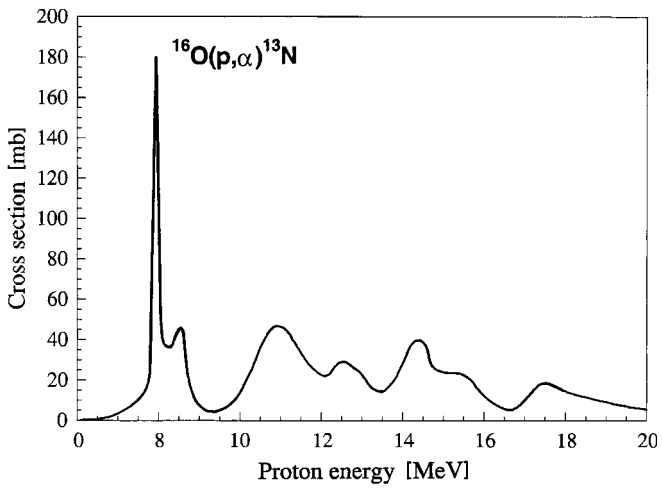


**Fig. 1.** Excitation function of the $^{16}$O($p$, $\alpha$)$^{13}$N reaction. Data adopted from [14].

**Table 4.** Routine methods of production of some commonly used photon emitters [10, 13].

| Radionuclide | $T_{1/2}$ | Mode of decay (%) | Main $\gamma$-ray energy in keV (%) | Production data | | |
|---|---|---|---|---|---|---|
| | | | | Nuclear reaction* | Energy range (MeV) | Thick target yield MBq(mCi)/μA · h |
| $^{67}$Ga | 3.26 d | EC (100) | 93 (37)<br>185 (20) (199.6) | $^{68}$Zn ($p$, $2n$)<br>$^{67}$Zn ($p$, $n$) | 26 → 18 | 185 (5) |
| $^{99}$Mo<br>↓ (generator) | 2.75 d | $\beta^-$ (100) | 181 (6)<br>740 (12) | $^{235}$U ($n$, $f$)<br>$^{98}$Mo ($n$, $\gamma$) | | [a]<br>[b] |
| $^{99m}$Tc | 6.0 h | EC (100) | 141 (87) | | | |
| $^{111}$In | 2.8 d | EC (100) | 173 (91)<br>247 (94) | $^{112}$Cd ($p$, $2n$)<br>$^{111}$Cd ($p$, $n$) | 25 → 18 | 166 (4.5) |
| $^{123}$I | 13.2 h | EC (100) | 159 (83) | $^{123}$Te ($p$, $n$)<br>$^{124}$Te ($p$, $2n$)<br>$^{127}$I ($p$, $5n$)$^{123}$Xe [c]<br>$^{124}$Xe ($p$, $x$)$^{123}$Xe [c] | 14.5 → 10<br>26 → 23<br>65 → 45<br>29 → 23 | 137 (3.7)<br>392 (10.6)<br>777 (21) [d]<br>414 (11.2) [d] |
| $^{201}$Tl | 3.06 d | EC (100) | 69 – 82 (X-rays)<br>166 (10.2) | $^{201}$Tl ($p$, $3n$)$^{201}$Pb [e] | 28 → 20 | 18 (0.5) [f] |

* Evaluated excitation functions of all the reactions listed here (except the neutron induced reactions) are now available in [21]. The yields given here are generally in agreement with those reported in [21].
a: TBq (hundreds of Ci) amounts of this radioisotope are produced at centres with well-developed technology.
b: Method used in less-developed laboratories.
c: $^{123}$Xe decays by EC (87%) and $\beta^+$ emission (13%) to $^{123}$I.
d: This is $^{123}$I yield expected from the decay of $^{123}$Xe over an optimum time of about 7 h.
e: $^{201}$Pb decays by EC (100%) to $^{201}$Tl.
f: This is $^{201}$Tl yield expected from the decay of $^{201}$Pb over an optimum time of 32 h.

cases machines accelerating four particles, viz. $p$, $d$, $^3$He and $\alpha$-particles, have proven to be very versatile. Evidently, the development of a production process involves considerable amount of nuclear data work.

*Photon emitters*

A large number of $\gamma$-ray emitting radionuclides have found application in diagnostic nuclear medicine using either $\gamma$-cameras or, in recent years, SPECT. The most commonly used SPECT radionuclide $^{99m}$Tc ($T_{1/2} = 6.0$ h) is produced using a nuclear reactor (see above). Several other SPECT radionuclides, produced at a cyclotron, are listed in Table 4. All of them need a medium-sized cyclotron, although in some cases (e.g. $^{67}$Ga, $^{111}$In and $^{123}$I) low-energy machines capable of inducing ($p$, $n$) reactions have also been used [18–20]. The nuclear reaction cross section data for most of the processes are known and have been recently evaluated, using both nuclear model calculations and fitting methods [21]. Surprisingly the data for the commonly employed $^{124}$Xe($p$, $x$)-process for the production of $^{123}$I, a widely used SPECT radionuclide, are still discrepant.

### 3.2.3 On the possibility of accelerator production of $^{99}$Mo/$^{99m}$Tc

There has been some apprehension regarding the continued availability of the most commonly used SPECT radionuclide $^{99m}$Tc. With the closure of ageing nuclear reactors, the supply of $^{99}$Mo, the parent of $^{99m}$Tc, may be jeopardised. Some thoughts were therefore devoted to a possible production of $^{99}$Mo and $^{99m}$Tc at a cyclotron. In a report Lagunas-Solar *et al.* even claimed [22] that medium-sized cyclotrons could partly or wholly replace

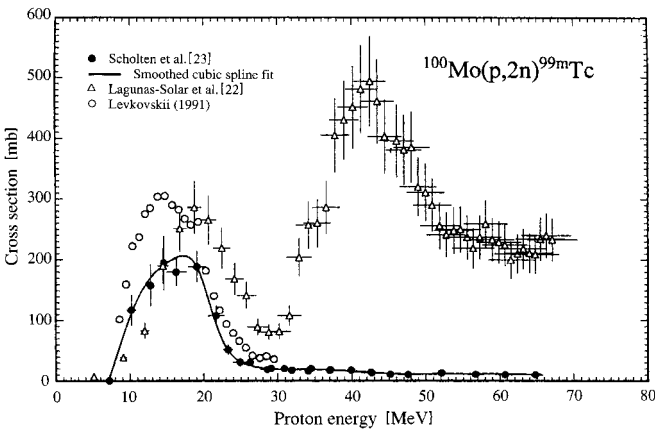


**Fig. 2.** Excitation function of the $^{100}$Mo($p$, $2n$)$^{99m}$Tc reaction. Diagram taken from [23]. The strong peak at about 42 MeV reported in [22] was not observed by authors of [23], who used highly enriched $^{100}$Mo as target material.

reactors, as far as the production of $^{99}$Mo/$^{99m}$Tc is concerned. This claim was based on the exceptionally high $^{98}$Mo($p$, $\gamma$)$^{99m}$Tc and $^{100}$Mo($p$, $2n$)$^{99m}$Tc reaction cross sections found by them. Under an IAEA-sponsored study, done mostly at Jülich, Scholten *et al.* [23] performed some key measurements using several cyclotrons. The cross section of the $^{98}$Mo($p$, $\gamma$)$^{99m}$Tc reaction was found to be negligibly small ($< 0.2$ mb) over the whole investigated energy range of 6 to 45 MeV, and the results of measurements on highly enriched $^{100}$Mo are given in Fig. 2. The peak in the cross section at about 17 MeV is due to the $^{100}$Mo($p$, $2n$)$^{99m}$Tc reaction. This was attributed by Lagunas-Solar et al wrongly to the $^{98}$Mo($p$, $\gamma$)$^{99m}$Tc process. The second strong peak at about 42 MeV reported by

Lagunas-Solar *et al.* could not be observed in the work of Scholten *et al.* [23]. Presumbly it was due to some impurity. The study of Scholten et al led to the conclusion that $^{99m}$Tc can be produced at a cyclotron in small amounts for local use only. The amount of $^{99}$Mo produced is small and its specific radioactivity rather low. There is thus no substitute for reactor produced $^{99}$Mo/$^{99m}$Tc generators. Some recent measurements done with deuterons under a Debrecen/Brussels cooperation lead to a somewhat similar conclusion.

In the meantime the situation has rather eased off since some new facilities for production of fission $^{99}$Mo have been established. Nonetheless, the results quoted above and the discussion based on them demonstrate the importance of accurate cross section measurements. Inaccurate and unreliable data can lead to erroneous interpretations and unnecessary controversies.

Despite the above mentioned negative remarks regarding the possibility of $^{99m}$Tc production at a small- or medium-sized cyclotron, it should be pointed out that the accelerator production of $^{99}$Mo/$^{99m}$Tc is not completely uninteresting. If a high-energy proton accelerator would be available, that could be utilized to produce spallation type neutrons, the fission of $^{235}$U could be used to produce $^{99}$Mo in large quantities.

### 3.2.4 Some special considerations in nuclear data studies

In research and development work relevant to production of radioisotopes at a cyclotron, following aspects need to be taken into account.

*Search for alternative production routes*

The development of an alternative production route may be necessary due to one or more of the following reasons:

(i) availability of a single accelerated particle at the cyclotron and constraint of its energy
(ii) demand on higher yield and purity of the product
(iii) demand on higher specific radioactivity.

A few examples are given in Table 5. In those and many other cases an alternative production route demands the use of a highly enriched target isotope whose natural abundance may be very low. The development of the $^{124}$Xe$(p, x)^{123}$Xe $\rightarrow$ $^{123}$I process demonstrates the changing demands on the quality of the medically important radionuclides. The natural abundance of $^{124}$Xe is only about 0.1%; consequently the highly enriched $^{124}$Xe is very expensive. What has become a common production technique today, was not imaginable about 20 years ago.

*Need of accurate data near reaction thresholds*

With the increasing use of low-energy cyclotrons in medical radioisotope production programmes, the importance of cross section data near reaction thresholds has enhanced. Many of the older data are based on excitation function measurements in which the incident particle energy was rather high. Due to energy degradation in the stacks over large spans, the experimental cross section data near the reaction thresholds may be inaccurate. The theory may provide here some guidance since the threshold is calculated rather accurately in comparison to the maximum cross section. A good example is furnished by a recent measurement on the excitation function of the $^{124}$Te$(p, n)^{124}$I reaction [24]. Due to rather poor existing data at $E_p \leq 12$ MeV, this reaction was considered to be unsuitable for production of $^{124}$I. The new measurements [24] showed that the threshold of the reaction is about 2.5 MeV lower. Hence this process can be conveniently used for the production of $^{124}$I at a small-sized cyclotron.

*Influence of increasing incident particle energy*

It is known that with increasing incident particle energy the number of competing reaction channels increases; the need of nuclear data, therefore, increases correspondingly. Of more significance are the reactions leading to the formation of isotopic impurities, since the non-isotopic impurities can be removed by a chemical separation. As an example, the data for the $^{75}$As$(p, xn)^{75,73,72}$Se reactions [25, 26] are shown in Fig. 3. For the production of the $\beta^+$ emitting $^{73}$Se ($T_{1/2} = 7.1$ h) the energy region $E_p = 40 \rightarrow 30$ MeV appears to be most useful. Over this energy range the yield of $^{73}$Se amounts to 1400 MBq/μA h and the level of $^{72,75}$Se impurity to $< 0.2$%. Evidently, the higher the projectile energy is, the more are the data needs. At high energies ($E_p > 200$ MeV) the spallation process occurs. It leads to a large number of products. The data needs are high, and the chemical processing effort involved is extensive.

**Table 5.** Development of alternative production routes.

| Radionuclide | Common production route | Alternative production route | Natural abundance of target (%) | Enrichment used (%) | Reason for alternative route |
|---|---|---|---|---|---|
| $^{15}$O | $^{14}$N $(d, n)$ | $^{15}$N $(p, n)$ | 0.37 | 99 | Small-sized cyclotron with only $p$ beam |
| $^{18}$F | $^{20}$Ne $(d, \alpha)$ | $^{18}$O $(p, n)$ | 0.20 | 98 | |
| $^{38}$K | $^{35}$Cl $(\alpha, n)$ | $^{38}$Ar $(p, n)$ | 0.06 | 96 | |
| $^{123}$I | $^{124}$Te $(p, 2n)$ $^{127}$I $(p, 5n)^{123}$Xe $\rightarrow$ | $^{124}$Xe $(p, x)^{123}$Xe $\rightarrow$ | 0.10 | 99.9 | Demand on purity |
| $^{186}$Re | $^{185}$Re $(n, \gamma)$ | $^{186}$W $(p, n)$ | 28.60 | 99.8 | Demand on high specific activity |

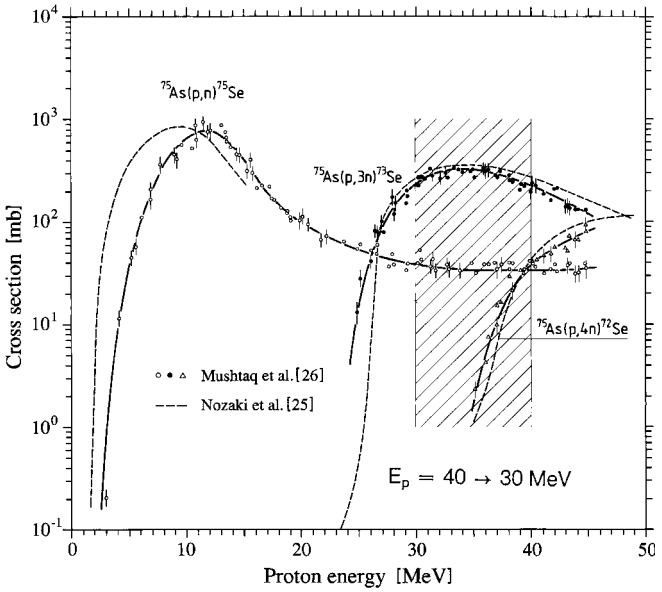


**Fig. 3.** Excitation functions of $^{75}$As$(p, xn)^{75,73,72}$Se nuclear reactions, depicting the influence of the increasing projectile energy. The optimum energy range for the production of $^{73}$Se is $E_p = 40 \rightarrow 30$ MeV. Diagram adopted from [26].

*Isomeric impurities*

The commonly used cyclotron radionuclides (positron emitters, SPECT radioisotopes like $^{123}$I, $^{201}$Tl, etc.) are isotopes without any other measurable isomeric state. Many of the potentially interesting research related radionuclides, on the other hand, consist of two isomeric states. If one of the states is short-lived and decays out by the time of application of the longer-lived isomer, there is no problem. However, if only the shorter-lived isomer is of interest, there may be some difficulty in resolving the decay curves and keeping the radiation dose to the minimum level. Two interesting examples which have emerged in recent years are $^{94m,g}$Tc and $^{120m,g}$I.

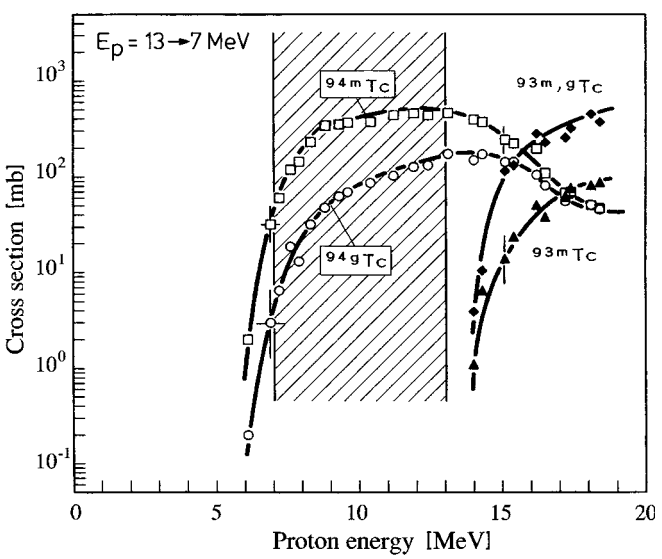


**Fig. 4.** Excitation functions of $^{94}$Mo$(p, xn)$-processes leading to the formation of $^{94m}$Tc, $^{94g}$Tc, $^{93m}$Tc and $^{93m,g}$Tc. The optimum energy range for the production of $^{94m}$Tc is $E_p = 13 \rightarrow 7$ MeV; the isomeric impurity $^{94g}$Tc, however, cannot be altogether eliminated. Diagram adopted from [27].

In the former case the metastable state $^{94m}$Tc$(T_{1/2} = 53$ min) is interesting and the ground state $^{94g}$Tc$(T_{1/2} = 4.9$ h) is the disturbing radionuclide. In the latter case, the ground state $^{120g}$I$(T_{1/2} = 1.4$ h) is important and the metastable state $^{120m}$I$(T_{1/2} = 53$ min) disturbs. The two radionuclides of interest can be produced via various routes. In each case it is important to know the isomeric cross section ratio.

The measured excitation functions of the $^{94}$Mo$(p, n)^{94m,g}$Tc and $^{94}$Mo$(p, 2n)^{93m,g}$Tc reactions [27] are shown in Fig. 4. Whereas the isotopic impurities $^{93m,g}$Tc can be eliminated from $^{94m,g}$Tc by a careful selection of the proton energy range within the target, even over the optimum energy range of $E_p = 13 \rightarrow 7$ MeV the $^{94g}$Tc/$^{94m}$Tc ratio is constant at 0.07, i.e. the 7% $^{94g}$Tc impurity cannot be eliminated. A change in the ratio was effected only by the use of another nuclear reaction, e.g. $^{93}$Nb$(^3$He,$2n)^{94m,g}$Tc or $^{92}$Mo$(\alpha, pn)^{94m,g}$Tc. In the case of the isomeric pair $^{120m,g}$I, three reactions, namely $^{122}$Te$(p, 3n)^{120m,g}$I, $^{120}$Te$(p, n)^{120m,g}$I and $^{120}$Te$(d, 2n)^{120m,g}$I, were investigated. The level of the $^{120m}$I impurity in $^{120g}$I was found to be the lowest in the $^{120}$Te$(p, n)$-process [28]. Evidently, the development of new radioisotopes, especially if they contain isomeric states, involves considerable amount of fundamental nuclear chemistry work.

### 3.2.5 Status of cross section data and integral tests

In comparison to the data for radionuclide production via neutron induced reactions in a nuclear reactor, the data for charged particle induced reactions at cyclotrons and accelerators have not been evaluated in much detail. Although the body of available data is not small [cf. 29, 30], not much effort has been devoted to the evaluation methodology of charged particle data. Only recently the most common reactions for the production of widely used $\beta^+$ and $\gamma$-emitters have been considered in the framework of an IAEA Coordinated Research Programme (CRP). Theory was found to be of limited use, so the major emphasis was on fitting procedures. The thus evaluated data are now available for the reactions considered [14, 21]. Data testing via integral yield measurements under well-defined conditions should be the next step. This has, however, so far not been done.

Besides the well-established diagnostic radionuclides, several non-conventional, research type radionuclides are gaining enhanced worldwide attention [cf. 31]. The development of production methods of those radionuclides demands detailed nuclear data work, covering both experimental investigations and nuclear model calculations.

## 3.3 Role of nuclear model calculations

Nuclear model calculations are of considerable interest in medical radioisotope production programmes, in particular with regard to their predictive power in case of unknown cross sections. In the energy region up to 20 MeV, the statistical model using the Hauser-Feshbach formalism has been very successful. At higher energies the precompound-hybrid model has been commonly applied.

The reactor production of radionuclides involves neutron induced reactions up to 20 MeV. Most of the reaction cross sections can be described fairly well by the theory.

As far as unknown cross sections are concerned, the predictive power of the theory, especially in combination with the known cross section systematics, is high. In the case of cyclotron production of radionuclides, a large number of reaction channels in various mass regions are involved. Nuclear model calculations are only partly successful in reproducing the production cross sections. In the light mass region, for example, which is of paramount importance in PET, theory cannot help. In the medium and heavy mass regions, on the other hand, especially the $(p, xn)$ and $(d, xn)$ reaction products can be described very well up to incident particle energies of about 50 MeV (cf. contribution by Shubin, this issue). In particular, the calculated data may be useful in adjusting the reaction thresholds since many of the experimental curves are rather erroneous near the thresholds (see above). In case of other reactions, such as $(p, \alpha)$, $(d, pxn)$, $(^3\mathrm{He}, xn)$, $(\alpha, xn)$ etc., considerable deviations may occur between experimental and calculated data [cf. 32, 33]. At energies above 50 MeV, even the simple $(p, xn)$ and $(d, xn)$ reactions are not reproduced well by the theory. On the other hand, it needs to be emphasized that the calculated data may have sufficient accuracies in connection with neutron and proton therapy (cf. contribution by Chadwick, this issue). The accuracies required in the isotope production work are more stringent and hence more emphasis is placed on experimental data.

In contrast to total cross section of a reaction channel, the calculation of a partial cross section, i.e. the probability of formation of an isomeric state, is more demanding since full information on nuclear structure has to be fed in. The excitation functions for the formation of isomeric impurities, therefore, cannot be predicted by theory only, and supporting experimental studies are essential. As an example, the results [34] for the isomeric pair $^{120m,g}$I are shown in Fig. 5. The $\sigma_m/\sigma_g$ ratio in the $^{122}\mathrm{Te}(p, 3n)^{120m,g}$I-reaction was determined experimentally and also calculated using the code STAPRE. The ground state ($T_{1/2} = 1.4$ h) has a spin ($2^+$); the spin of the metastable state ($T_{1/2} = 53$ min), however, is not known with certainty. The calculated results for various spin values of the metastable state suggest that its true spin is probably ($4^+$) or ($4^-$). Best results were obtained by assuming the energy of the metastable state as 550 keV (as against 900 keV given in the literature) and its spin as ($4^+$). With the latter two assumptions the $\sigma_m/\sigma_g$ ratio could be reproduced also in $^{120}\mathrm{Te}(p, n)^{120m,g}$I and $^{120}\mathrm{Te}(d, 2n)^{120m,g}$I processes. In medical radioisotope development work involving formation of isomeric states, therefore, besides careful experimental work, also a detailed knowledge of the level structure is required to be able to perform reliable nuclear model calculations to verify and validate the measured data.

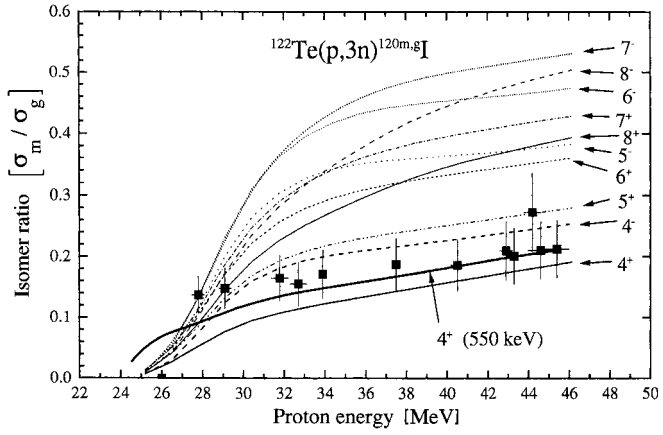


**Fig. 5.** Isomeric cross section ratio ($\sigma_m/\sigma_g$) for the isomeric pair $^{120m,g}$I in $^{122}\mathrm{Te}(p, 3n)$-reaction as a function of proton energy. Experimental data are shown as symbols and theoretical results as curves. The calculational results appear to be strongly dependent on the excitation energy of the metastable state, its spin and parity. Diagram taken from [34].

## 4. Conclusions

Nuclear data play a very important role in the choice and medical application of a radioisotope. The nuclear structure and decay data determine the suitability of a radioisotope for diagnostic application and the reaction cross section data its possibility of production in a pure form. Both reactors and cyclotrons are used for production purposes. The cross section data for reactor production are generally well-known and can be satisfactorily reproduced by nuclear model calculations. The cyclotron production, on the other hand, demands an extensive database, which is rather good in the case of the commonly used $\beta^+$ and single photon emitting radionuclides. The production of non-conventional radionuclides, however, puts some demands on data measurements as well as technical and radiochemical developments. In this context, longer-lived $\beta^+$ emitters are gaining increasing importance. Many of the new radionuclides under consideration consist of two or more isomeric states. Detailed measurements on isomeric cross section ratios in all the possible reaction channels are necessary to be able to choose a process which gives the lowest isomeric impurity. Nuclear model calculations can reproduce the experimental data on $(p, xn)$ and $(d, xn)$ reactions on medium mass target nuclei in the projectile energy range from threshold up to about 50 MeV. All the reactions in the light mass region, uncommon reactions (like $(p, \alpha)$) in various mass regions, and isomeric cross section ratios cannot be properly treated by the theory. In all those cases experimental studies are mandatory.

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